



Complete Summary

GUIDELINE TITLE

Treatment with fludarabine for patients with follicular and other low grade Non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia.

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. MacEachern J, Chin-Yee I, Imrie K, Esmail R, Makarski J, Meyer RM. Treatment with fludarabine for patients with follicular and other low grade non-Hodgkin's lymphoma and Waldenstrom's macroglobulinemia [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2001 Nov. 18 p. (Practice guideline report; no. 6-2). [31 references]

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

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SCOPE

DISEASE/CONDITION(S)

Advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia
- To evaluate the toxicities of fludarabine

TARGET POPULATION

Adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom's Macroglobulinemia who require therapy; patients who require initial therapy, or who have been previously treated, are considered.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Fludarabine
2. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone (CVP); or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, doxorubicin, teniposide, and prednisone (CHVP), plus interferon; cyclophosphamide, doxorubicin, vindesine and prednisone (CHEP) or rituximab

MAJOR OUTCOMES CONSIDERED

Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

An initial literature search was conducted in February 2000 and included the following databases: MEDLINE (1985 to February 2000), CANCERLIT (1985 to January 2000), and the Cochrane Library (Issue 4, 1999). The following terms were used for MEDLINE and CANCERLIT: "exp lymphoma": (Medical subject heading [MeSH], title) combined with "fludara:" (title) or "fludarabine" (text word). The results were limited to human and English language. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), PUBMED, and conference proceedings of the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) published in 1997–1999 were searched for reports of

new or ongoing trials. Reference lists from relevant articles were searched for additional trials.

An updated literature search of the MEDLINE (March 2000 to June 2001) and CANCERLIT (March 2000 to March 2001) databases was conducted in June 2001. This update also included searches of the Cochrane Library (Issue 2, 2001), PDQ, and the 2000 ASH and 2000–2001 ASCO conference proceedings.

These same sources were searched to locate studies evaluating the role of fludarabine in Waldenstrom's Macroglobulinemia. The search terms used in MEDLINE (1985 to June 2001) and CANCERLIT (1975 to March 2001) were: "exp waldenstrom macroglobulinemia": (MeSH and title) combined with "fludara:" (title) or "fludarabine" (text word). The search was limited to human and English language. In addition to the 2000 ASH and 2000–2001 ASCO conference proceedings, the 1997–1999 proceedings were also searched for Waldenstrom's Macroglobulinemia.

Article Assessment

Abstracts of relevant articles obtained from the February 2000 systematic literature search were blinded for author, institution, and whether the results were positive or negative. Two reviewers then independently assessed the blinded papers for inclusion. Reviewers were also unaware of whether the studies were published in journal or in abstract form. A Kappa of 0.7 or greater was predetermined to be acceptable. Where there was a discrepancy between the reviewers' opinions, the reviewers discussed the individual blinded studies and decided whether to include or exclude the paper based on the preset inclusion criteria. The lead author of this guideline determined the eligibility of citations identified with the updated literature search of June 2001.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were one of the following:

1. Randomized controlled trials comparing fludarabine either as monotherapy or in combination with other treatment alternatives in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia. Primary outcomes of interest included survival, progression-free survival, or quality of life.
2. Reports of fludarabine-related toxicity in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia.
3. Economic evaluations comparing fludarabine to other treatment alternatives in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia.

Exclusion Criteria

1. Trials of less than 10 patients (but individual case reports of toxicity were included).
2. Trials including fludarabine as part of a high-dose chemotherapy and/or transplant protocol.

NUMBER OF SOURCE DOCUMENTS

From the initial literature search of February 2000, 23 publications were assessed as meeting the eligibility criteria and included six randomized controlled trials, three economic evaluations, one quality of life analysis, and 13 toxicity reports.

The updated search of June 2001 identified an additional seven citations: three randomized controlled trials, one update reporting quality of life outcomes, one economic analysis, and two toxicity reports.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Due to the heterogeneity of the treatment regimens compared with fludarabine, the varied use of fludarabine as either a single agent or as part of a combination regimen, and the lack of consistency in reporting the outcomes of interest, there was no attempt to pool efficacy data. Treatment-related toxicity data were summarized in the Adverse Events section of the original guideline document.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Hematology Disease Site Group (DSG) considered differences in survival and quality of life to be important outcomes upon which treatment recommendations could be based. The DSG also discussed the use of surrogate outcomes, such as response rate and progression-free and treatment-free survivals as proxies for overall survival and quality of life. As improved, progression-free survival may be a desirable goal for some patients and may translate into improved quality of life, it was considered to be a potentially useful outcome for determining a treatment recommendation. Treatment-free survival may also be a reasonable proxy measure for quality of life, as it is assumed that disease progression necessitating therapy would be associated with clinically important symptoms, and deferring any treatment-related toxicity would be valued. However, there may be a bias in measuring this outcome, as none of the randomized trials described were blinded for treatment allocation. Knowing that patients were previously unexposed to

fludarabine could favour the re-initiation of fludarabine therapy in patients previously allocated to standard therapy. Treatment-free survival was, therefore, considered in conjunction with progression-free survival in making recommendations. Response rate was felt to be an inadequate surrogate marker upon which to base a treatment recommendation and an outcome more appropriately used in trials reporting results of preliminary new drug testing. Response rate has been included in this report to assist in interpreting progression-free survival when this latter outcome has been reported only in those patients demonstrating a response.

In considering patients with previously untreated low grade lymphoma, the DSG gave greatest weight to the trial comparing fludarabine with cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon (CHVP-IFN). As this trial showed a difference in all efficacy outcomes, including survival, in favour of the CHVP-IFN group, it was concluded that there was insufficient evidence to support using fludarabine as initial therapy. The DSG recognized that CHVP-IFN is not considered a standard treatment in Ontario. It is generally believed that CHVP and cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) result in similar outcomes. Furthermore, other than for the potential that more rapid responses are seen in some patients treated with CHOP, it is generally believed that CHOP and cyclophosphamide, vincristine, and prednisone (CVP) produce similar outcomes. With respect to the addition of IFN to chemotherapy, the DSG is aware of the uncertainty of the role of this agent and is in the process of completing a guideline assessing IFN in patients with follicular and other low grade lymphomas. As a result, the DSG concluded that CHVP-IFN may be comparable to the standard regimens (CVP and CHOP) used in Ontario for such patients. The DSG acknowledges the potential risks of drawing these conclusions. The possibility that the risk criteria used in this study may lead to the inclusion of patients with occult transformed lymphoma is also recognized. Such patients may have superior outcomes with CHVP-IFN due to treatment that includes doxorubicin. Separate studies are needed to compare fludarabine with a standard therapy in lower risk patients.

In patients with previously treated low grade lymphoma, the one randomized trial in which fludarabine was compared with a standard option (CVP) demonstrated superior progression-free and treatment-free survival and improvement in one-quality-of life domain (social function) in patients receiving fludarabine; no difference in survival was detected. These data were considered sufficient to warrant a recommendation supporting the use of fludarabine as an acceptable treatment option for these patients.

The trial comparing fludarabine with cyclophosphamide, doxorubicin, prednisone (CAP) in patients with previously treated Waldenström's Macroglobulinemia showed that fludarabine was associated with superior responses, progression-free survival in responding patients and treatment-free survival in all patients, both with reduced toxicity. Although each of these individual outcomes would be considered as having limitations in leading to a recommendation, the sum of these findings, along with the preliminary suggestion of superior quality of life as assessed by a Q-TWiST analysis, resulted in the conclusion that fludarabine was an acceptable treatment option.

Finally, the DSG recognizes that the role of monoclonal antibody therapies, such as rituximab, will need to be included in any subsequent determinations of the sequence of therapies for these patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The four economic evaluations identified in the literature search were considered to be preliminary and of a hypothesis-generating nature. These reports did not explicitly indicate the payer perspective of the analyses, did not adequately describe the process used to ensure that the competing treatment options were provided to similar patient groups, and did not include an explicit statement regarding which direct and indirect costs were measured. They appeared to be heavily weighted by the drug acquisition charges rather than by measuring costs. Treatment efficacy outcomes were either assumed to be equivalent or were not considered. Based on these limitations, these data were considered to be insufficient to contribute to conclusions and recommendations.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 178 clinicians (100 medical oncologists and 78 hematologists) in Ontario. The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (second mailing of the complete package). The Hematology Disease Site Group (DSG) reviewed the results of this survey.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Previously Untreated Patients with Stage III–IV Low Grade Lymphoma

There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone;

cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgment. Choice of treatment should take into account factors such as route of administration, risk of infection, and outcomes of interest.

Previously Treated Patients with Stage III–IV Low Grade Lymphoma

Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgment, and drug availability and should take into account factors such as the route of administration, the risk of infection, and outcomes of interest.

Patients with Waldenström's Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, teniposide, and prednisone, plus interferon, in a randomized trial involving 131 previously untreated patients ages 60 to 75 years, with follicular lymphoma and at least one high-risk feature. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus 63%, $p < 0.05$) and two-year survival (62% versus 77%, $p < 0.05$).
- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 309 previously untreated patients with diffuse small lymphocytic and follicular small cleaved or mixed cell lymphoma. Respective median progression-free survivals were 494 and 396 days (p value not

given). Too few events had occurred to allow for an assessment of overall survival.

- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients receiving fludarabine had a superior two-year progression-free (32% versus 14%; $p = 0.028$) and two-year treatment-free survival (41% versus 20%; $p = 0.034$). No difference in two-year overall survival was detected (70% versus 75%; $p = 0.738$). This study also assessed quality of life and demonstrated superior social function in patients receiving fludarabine.
- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, and prednisone in a randomized trial reported in preliminary abstract form involving 92 patients with Waldenstrom's Macroglobulinemia who were either refractory to or relapsed from initial alkylator-based therapy. Response was superior in patients receiving fludarabine (28% versus 11%; $p = 0.019$). Superior progression-free survival in responding patients ($p = 0.02$) and treatment-free survival in all patients ($p = 0.04$) were also observed with fludarabine. No difference in survival was detected.

POTENTIAL HARMS

Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, and prednisone in a randomized trial reported in preliminary abstract form involving 92 patients with Waldenstrom's Macroglobulinemia who were either refractory to or relapsed from initial alkylator-based therapy. Fludarabine was associated with less mucositis and alopecia; no differences in other toxicities were detected. Using a Q-TWiST analysis, patients receiving fludarabine spent more time without symptoms of disease or treatment toxicity (5.9 months; $p = 0.006$).

Hematologic

Myelosuppression is a side effect of fludarabine. Profound lymphopenia and mild to moderate neutropenia and thrombocytopenia can occur. Although myelosuppression is the most common side effect, Eastern Cooperative Oncology Group (ECOG) grade 3 or greater hematologic toxicity is seen in 3.8% and 5% of treatment courses in previously untreated lymphoma patients.

Opportunistic Infection

From the randomized trials, grade 3–4 clinical infection is observed in 1 to 2% of patients receiving fludarabine with no significant differences detected when compared with fludarabine plus idarubicin; cyclophosphamide, vincristine, and prednisone (CVP); or cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon (CHVP-IFN) in previously untreated lymphoma patients. In previously treated lymphoma patients, fludarabine was associated with more infections in comparison with CVP.

Autoimmune Phenomena

Autoimmune hemolytic anemia (AIHA) has been reported in as many as 7.5% of low grade lymphoma patients undergoing treatment with fludarabine; 50% of

these patients had a history of AIHA. Unlike chronic lymphocytic leukemia (CLL), AIHA may correlate with disease progression in patients with low grade lymphoma. Because fludarabine has been reported to exacerbate or precipitate AIHA, the manufacturer considers AIHA to be a contraindication for using fludarabine (Practice Guideline Report #6-1). Autoimmune thrombocytopenia has also been reported.

Graft-versus-Host Disease

Transfusion-related graft-versus-host (GVH) disease has been anecdotally reported as occurring up to 11 months after treatment with fludarabine. The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products when these products contain viable lymphocytes (e.g., red cell or platelet concentrates).

Tumour Lysis Syndrome

Although fludarabine-associated tumour lysis syndrome has been more typically described in patients with chronic lymphocytic leukemia (CLL), it has also been reported in low grade lymphoma.

Neurological

Peripheral neuropathy developed in 5 patients, all of which completely resolved within 5 weeks in one randomized controlled trial and was found to be more frequent with CVP in another. Five cases of unusual neurological illness were reported in fludarabine-treated patients with low grade non-Hodgkin's lymphoma. Neurological toxicity is dose limiting, and the dose of fludarabine should not exceed the recommended dose.

Other

Nausea, vomiting, and mucositis are infrequent and occur less frequently with fludarabine than with CVP. Fludarabine does not cause alopecia and is not toxic to the kidneys or heart. Transient grade 2 hepatic toxicity has been observed. Individual cases of fatal fulminant myelofibrosis, fatal bone marrow necrosis, and seropositive symmetrical inflammatory polyarthritis have been reported following fludarabine use in patients with indolent lymphoma. A single patient with low grade lymphoma was reported to have developed progressive epidermal necrolysis following a second cycle of fludarabine; the syndrome was successfully treated with high dose steroids, cyclophosphamide, and immunoglobulins. There have been individual case reports of Guillain-Barré syndrome in a patient with Waldenström's Macroglobulinemia, fatal miliary tuberculosis in a patient with high grade lymphoma, and cryptococcal meningitis plus intracranial tuberculoma 18 months after completion of treatment in a patient with Waldenström's Macroglobulinemia.

CONTRAINDICATIONS

CONTRAINDICATIONS

Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell-mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
- The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
- Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. MacEachern J, Chin-Yee I, Imrie K, Esmail R, Makarski J, Meyer RM. Treatment with fludarabine for patients with follicular and other low grade non-Hodgkin's lymphoma and Waldenstrom's macroglobulinemia [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2001 Nov. 18 p. (Practice guideline report; no. 6-2). [31 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Nov 7

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Treatment with fludarabine for patients with follicular and other low grade Non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2): 502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 29, 2004. The information was verified by the guideline developer on July 19, 2004.

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The logo for FIRSTGOV, with "FIRST" in blue and "GOV" in red, and a small red star above the "I".

